A REVIEW OF THE SERUM TREATMENT OF INFECTIOUS DISEASES IN THE PRACTICE OF THE CITY OF GLASGOW FEVER AND SMALL-POX HOSPITALS, BELVIDERE.

By JOHN BROWNLEE, M.A., M.D., D.Sc.Glasg.,
Physician-Superintendent, City of Glasgow Fever Hospital, Belvidere.

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Physician-Superintendent, City of Glasgow Fever Hospital, Belvidere.

THE serum treatment of disease began in the last decade of last century with the discovery of the antitoxin for diphtheria, and in Belvidere Fever Hospital this treatment was inaugurated in the year 1894. Since that time not only this serum, but a very large number of others have been tried, and I propose in this paper to give a short description of the results obtained in this hospital by the use of these different remedies. In general it may be said that the first discovered, namely, the diphtheria antitoxin, is up to the present moment much the most important, and that plague serum takes quite definitely the second place though at a considerable distance. Only occasionally are successful results obtained with the others, and these must be considered at present more or less in the light of favourable accidents.

With regard to the antitoxin for diphtheria, there is no doubt at all that it possesses very marked advantages, the specific membrane rapidly separating or dissolving under its use, and the toxic symptoms of the disease disappearing quickly. The great point, of course, is to give the remedy early, and a small dose given towards the beginning of the attack is of much more importance than a large one given later. This is sometimes, however, specially difficult to ensure, as the onset of diphtheria differs in many cases from that commonly seen in other specific fevers. A very considerable amount of membrane may be present for some days, but as no very marked symptoms exist a physician is not called in. Suddenly a change from a condition of apparent health to one of profound illness takes place, and haste is made to obtain assistance, but much irreparable damage has been done. In the earlier period antitoxin is of the greatest use in preventing the development of these serious symptoms, but in the later stage it is not nearly so valuable. I do not agree, however, with those who say that it possesses practically no curative effect on already poisoned tissues; I think that even in the severest cases there is an amelioration of the poisoning, not merely in the direction of preventing the continuance of the process, but in the actual disassociation of the poison from its combinations with the cells of the body. As regards dosage, on the first or second day 3,000 to 4,000 units are probably quite sufficient; later the amount given depends on the gravity of the case. The practice of the hospital is to give 6,000 units as a minimum and about 20,000 units as a maximum. It is also the custom to give what has to be given as far as possible in one dose, as the procedure is somewhat painful, and it is unfair to subject a child to the repetition of the process unless it is absolutely required. Serum is generally given subcutaneously. In the malignant cases, however, it is the custom here to administer it intravenously. Experimentally, intravenous administration has been shown to give animals the advantage of about eight hours over the subcutaneous method, and there is no doubt that in very severe cases, where the glands of the neck are greatly swollen, where oozing of blood from the nose and throat is taking place, or in those cases where a diphtheritic broncho-pneumonia is present, that serum, given intravenously, possesses some advantage over that given subcutaneously.

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[1] Read at a meeting of the Glasgow Southern Medical Society held on 28th November, 1907.

There are, however, some other points relating to the anti-diphtheritic serum not so generally appreciated. As regards its therapeutic value, different samples present great constancy. No maker's serum, however, produces quite uniform clinical results when used therapeutically. Between the chief different makers, taken over a series of years, there does not seem to be much difference, but between different samples of the same maker there has been frequently great variation. At times the serum has seemed an almost perfect remedy, and at other times next door to useless. Sometimes the therapeutic results have been so perfect that it seemed possible that the death-rate from diphtheria should not exceed 5 or 6 per cent; at other times with certain consignments of serum no beneficial result could be observed. These variations do not appear to be due to alteration in the type of the disease so much as to differences in the bodies contained in different consignments of the serum. It would seem that the poisons produced by the organism of diphtheria call forth a different response in man and in the horse. Though the chief poison of the diphtheria organism is easily neutralised by the specific antitoxin, yet there are probably a number of other poisons which act more powerfully on man, and for which the horse serum consequently contains very variable amounts of antibody. It must also be evident that when the potency of a serum is estimated by tests on one of the lower animals (in this case the guinea-pig), the therapeutic efficacy on man can hardly be expected to bear a constant relationship to the estimated value of the serum. This matter was brought before the International Congress of Demography last summer by Professor Krauss, of Vienna, and a committee appointed to consider it. The alteration in the type of the disease, on the other hand, cannot be wholly neglected. It is well known that diseases vary in type from time to time, and in consequence it seems probable that if the full advantage is to be obtained from the serum treatment of diphtheria, the serum should so far as possible be obtained by the use of cultures taken from cases as near as possible to the type specially predominant at the moment. The actual facts upon which these opinions are specially based are to some extent contained in the letters written two to four years ago printed at the end of this paper.

With regard to plague serum, there has not been any great experience since the last papers were published, but that little, combined with some experimental work, goes to verify the accuracy of the former conclusions, which are practically identical with those reprinted recently as the result of observations in India. Plague serum is of no use at all in any malignant case of plague; in fact if a person is likely to die in four or five days illness, I would be inclined to deny it any efficacy, but, if it appears that the resistance of the patient is likely to be sufficient to tide him over this period a cure would seem to be within the range of early treatment. The serum has some peculiarities which mark it off from the anti-diphtheritic serum. It is not so markedly antitoxic, but is chiefly bactericidal. Further, the anti-bacillary component passes with great difficulty through the lymphatic glands. Both by observations on man and on the rabbit it seems to be proved that not until three days after the hypodermic injection of the remedy are its full clinical effects to be expected, so that consequently it is necessary to inject large quantities (250 cubic centimetres) intravenously if the full benefit is to be obtained. In milder cases, however, the subcutaneous method was found sufficient if the serum was injected under the skin into the region of which the lymphatic vessels drain directly into the plague-infected bubo. This delay of absorption is a feature which, so far as I know, has not been pointed out, and as the phenomenon suggests the distribution of the remedy to the affected parts by living white cells, it has some interest from the point of view of immunity. To give the complete evidence on which this opinion is based is not possible in this paper, but one of the cases affords so complete a picture of the phenomenon that it is quoted here.

"N. T., female, æt. 10, admitted on 11th September, 1901, in the evening. Illness began on day prior to admission with severe headache and malaise. At the same time the right groin was complained of as being painful and tender, but the patient could walk. The temperature on admission was 102·8° F. The pulse numbered 128 per minute, and the respirations 26. The face was heavy looking and flushed. The pupils of the eyes were contracted and the conjunctivæ suffused. The lips were dry, as also the tongue, which was furred. A mottling on the skin was noted over the abdomen, flanks, arms, and legs. The spleen was slightly enlarged. A bubo, consisting of several enlarged lymphatic glands, was noted in the right groin. It was very tender. A smaller similar bubo also existed in the left groin. A plague pustule was observed on the left iliac crest, with a red areola of about three quarters of an inch in diameter. In the front of the left thigh a second though very small pustule was also noted. In the former, degenerated plague bacilli were observed and a typical growth obtained on culture. On the morning of 12th September the patient was somewhat worse. The buboes in both groins had advanced, but that in the right side was much the larger. Forty c.c. of Yersin's serum were injected into the subcutaneous tissue of the anterior aspect of the right thigh, and an additional 100 c.c. into the areolar tissue of the abdominal wall. Next day little change was seen in the patient's condition, but the bubo on the right side was much smaller and less tender to touch. The pustule over the left iliac crest was healing, but the one on the right leg developing. The latter was opened and dressed with a moist carbolic (1 in 40) dressing. On 14th September, the temperature was beginning to fall, but though the bubo in the right groin had greatly diminished and was no longer tender, that in the left had advanced in size. The glands above Poupart's ligament also now were involved. A good deal of œdema was present, and the skin was erythematous for an area of at least three inches in diameter. Forty c.c. of serum were injected into the subcutaneous tissue of the anterior aspect of the left thigh, and another 100 c.c. into the wall of the abdomen.

"By the evening, *i.e.*, nine hours afterwards, the œdema round the bubo had almost disappeared, and the glands above Poupart's ligament could be palpated without resistance. A gland behind the ramus of left jaw, however, had been felt for the first time in the early afternoon. It was painful to the touch, and resembled the first stage of an ordinary plague bubo. This bubo continued developing most of the next day, and then began to subside spontaneously.

"From this point improvement continued, and convalescence, though interrupted by a rather severe serum fever, was very good."

In addition to these two sera a great many others have been tried. During the small-pox epidemics the serum of vaccinated heifers was used in a considerable number of severe cases. The results of this were published at the time in the *Lancet*, and, as far as subcutaneous injection of the serum was concerned, were wholly negative. During the next epidemic, however, that of 1903-1904, it was determined by the late Professor R. S. Thomson to use the remedy intravenously in severe cases. As the amount of serum to be injected was considerable, only hæmorrhagic cases were selected for treatment. It was found that about 30 oz. of heifer serum could be injected into a vein without any deleterious result, the serum being allowed to flow in slowly by its own weight. The first patient on which it was tried was considered a typically hæmorrhagic case of small-pox by Professor Thomson and by other physicians who had had very considerable experience in the disease. The patient was on the fifth day of illness, with almost no appearance of the true eruption. The day after the injection the patient was immensely better, and a very copious true eruption had appeared all over his body. This eruption hardly continued to develop more than a couple of days, and dried up in the early vesicular stage. It is difficult to believe that the serum had not a marked influence in aborting this case, but it must be classed among the accidents of serum treatment, as in four other hæmorrhagic cases treated subsequently no effect at all was observed.

It may be noted here that the heifer serum used in these and in the previous cases was very much less toxic to the human subject than that of the horse, a rash following its use in only one case, and articular pains, &c., being wholly absent.

The results obtained with anti-streptococcic serum have not, on the whole, been very encouraging, and its use is at present given up. It was tried in a long series of septic scarlet cases, and also for some time in the puerperal fever wards. With scarlet fever in a few cases the effect seemed very beneficial. In some under my own personal care ulcerating throats of formidable appearance healed in a manner seldom seen in cases not so treated, but, on the other hand, nothing like constancy could be observed. Other throats clinically identical, and of which the bacterial flora seemed essentially the same, showed no sign of improvement, and my own experience in the use of this remedy was the same as that of the other members of the staff, which was described at the time in a paper by Dr. Campbell Marshall. In puerperal fever the remedy seemed even less efficacious, and its use was abandoned. Later on, however, when it became evident that the intravenous administration of serum was in some instances a more potent method, the treatment of puerperal fever by this means was attempted. The results again were wholly negative, and on one occasion it even seemed that the administration did harm.

Of the other sera tried, anti-coli, anti-typhoid, and anti-staphylococcus may be mentioned. In all these instances specific effects were absent. The anti-coli serum was introduced into the peritoneal cavity of some patients after operation for perforation in enteric fever in the hope that the subsequent peritonitis might be avoided, but without any apparent effect. One case treated by the anti-staphylococcus serum, however, deserves mention as throwing some light on the nature of the fortunate accidents in serum therapy. The patient on whom it was tried was admitted certified enteric fever. The illness had begun with head symptoms, which had, however, soon passed off, the patient continuing thereafter to exhibit daily rigors, with a temperature ranging from 102° F. to 104° F. On admission, nothing was discoverable even after the most careful examination. Head symptoms were quite absent, and the heart, lungs, and abdomen were free from any recognisable lesion. It was considered probable that a deep-seated abscess existed, and the case was thought a favourable one on which to try the remedy. After the first injection of 10 c.c. subcutaneously, the patient passed two days without a rigor; after a second injection, twenty-four hours passed without a rigor; while a third injection two days later produced no effect. For some days more the patient remained in the same condition. A swelling then began to appear at the base of the right ear posterior to the ramus of the jaw. The surgeon, Dr. Dalziel, after a consultation, operated. A localised periostitis of the petrous bone was found, and drained. After this no further rigor occurred, and the patient made an uninterrupted recovery.

Cultures made at the time of the operation gave a pure growth of the bacillus coli communis. In this case we have, therefore, an example of a non-specific therapeutic action.

The meaning of such accidental cures is not quite clear. In many cases they are probably merely coincidences, but the whole can hardly be explained in this way. It is more probable that these sera contain some easily destructible substances, the chemistry of which is at present unknown, and whose presence or absence can consequently not be tested. On the other hand, it is possible that the serum injected has, as Metchnikoff suggests, sometimes a stimulant action which calls forth fresh powers of resistance on the part of the patient. Something of the nature of an opsonin may also be contained in certain samples of serum, which may afford the patient a certain amount of aid in meeting the bacterial invasion.

As this note simply refers to the experience of Belvidere Hospital, it has been thought well to append a list of the papers published by members of the staff, in which the observations are detailed.

Appendix containing Letters on the Variation of Potency in Antidiphtheritic Serum.

15th November, 1904.

DEAR SIRS,—I return by this post the remainder of the last batch of serum which you sent. Contrary to our almost uniform experience, this has had almost no therapeutic effect at all, even mild cases showing no immediate improvement and the sera making little progress. One relapsed yesterday with a new attack of severe diphtheria, although 27,000 units were administered ten days ago. This is so exceptional, and the general want of effect produced by this consignment so marked, that I am led to believe that it has undergone some change or deterioration.—I am, Yours truly,

JOHN BROWNLEE.

Messrs. —— ——

25th November, 1904.

JOHN BROWNLEE, Esq., M.D.,
City of Glasgow Fever Hospital, Glasgow.

DEAR SIR,—With further reference to your favour of 15th November, respecting antidiphtheria serum, we beg to say that the supplies returned by you were promptly placed in the hands of Dr. ——, who has examined it, and we attach hereto his report. In the circumstances, we are unable to make any suggestions as to the cause of the results you observed, and shall be glad, if you have any theories upon the subject yourself, to have you make us acquainted with them. Of course, a large number of bulbs from this batch have been distributed in other quarters, and we have not received a single complaint, all of which appears to point to some peculiar conditions, or, perhaps, idiosyncrasy.

Thanking you in anticipation of your further advices.—We remain, Very truly yours,

—— ——

24th November, 1904.

DEAR SIRS,—I have examined the bulbs of serum which you forwarded to me as having been returned from the Belvidere Fever Hospital, bearing certificates dated :—

Batch No. 72, - - - 1st July, 1904.
Batch No. 74, - - - 24th August, 1904.

No. 72 is still sterile and contains 425 antitoxin units per c.c. as certified.

Batch 74 is also sterile and contains 450 antitoxin units per c.c. at certified.—Yours sincerely,

—— ——

1st December, 1904.

DEAR SIRS,—I have in hand your note, for which I beg to thank you. I am not surprised that on examination the samples of serum prove to have full strength. On a former occasion a consignment of serum which gave very unsatisfactory clinical results was also found to contain the normal amount of antitoxin. As your Mr. —— knows, I have for long suspected that a large part of the real curative value of the serum depends on some principle acting independently and in addition to the neutralising action of the antitoxin on the poison. About the relative failure in action there is no doubt. None of the cases have made the convalescence to which we are now accustomed. In all the cachexia has remained to a degree which recalls pre-antitoxin days; and in several patients conditions such as severe ulceration of the mouth are yet present. As I told you, in one case there was a very marked relapse, and this patient, who then received 12,000 units of other serum, is at the present moment the one who has made the best convalescence. I do not think that there was any peculiarity about the diphtheria. How to ascertain if my surmise as to the presence of some other principle than the antitoxin in the serum be correct or not is not clear. I have made a few experiments without definite result.—I am, Yours truly,

JOHN BROWNLEE.

Messrs. —— ——

3rd December, 1904.

JOHN BROWNLEE, Esq., M.D.,
City of Glasgow Fever Hospital, Glasgow.

DEAR SIR,—We thank you very much for your esteemed favour of the 1st inst., with regard to antidiphtheria serum, contents of which we have noted with much interest. We are taking the liberty of sending copies of this correspondence to our Biological Department at ———, as we feel sure that they will be interested in the suggestion you make as to the failure of this particular batch of antitoxin to produce the usual results under your administration. The fact that the case which relapsed, and then received 12,000 of another make of serum, has made the best convalesence, lends support to your suggestion that there was some peculiarity associated with the serum rather than with the patients or the particular type of the disease. Upon the other hand, the fact remains that the serum is always tested and standardised in connection with a true diphtheritic toxin, and if it neutralises this toxin in the guinea-pig we cannot see why it would fail to do the same in a human being. Moreover, as previously pointed out, no other complaints have reached us a result of the distribution of a large number of doses from the same batch, and in the present state of serum therapeutics it is hardly conceivable that an unsatisfactory batch would be employed over a large area without attracting attention in more than one quarter.

We shall be much interested in what our people in —— say upon this subject, and sincerely trust that eventually something definite may be ascertained in connection therewith. Particulars of any fresh information that you may at any time be able to give, will be very much appreciated.—We remain, Very truly yours,

—— ——

4th August 1906.

Dear Sirs,—At the present moment we are finding no sera for diphtheria really satisfactory, though I have no special fault to find with yours against any other. There is at present a change in the type of the disease and probably the organism. We have had more cases of paralysis following diphtheria in the last six months than in the preceding five years. I would suggest that you obtain strains of the organism from the localities to which you supply serum. That my experience is not solitary I see by a note in the *B. M. J.* of two weeks ago.—I am, Yours truly,

John Brownlee.

Messrs. —— ——

4th September, 1906.

Dr. John Brownlee,
Fever Hospital, Belvidere, Glasgow.

Dear Sir,

Re Antidiphtheria Serum.

With reference to your recent letter, we beg to say that we communicated the facts to our home laboratory, and their reply is just to hand. They write as follows:—

"The condition described is interesting; it may be of importance. Time and again it has occurred to us from this or that observation that it might be desirable to use a number of strains of diphtheria in our cultures, or different culture media, but we have hesitated to tamper with a procedure that apparently was so satisfactory as our production of antidiphtheria serum.

"Some suggestive work was done some two years ago by Dr. Vaughan, of the University of Michigan, wherein he sought to show that there was several toxins produced by the diphtheria germ, in particular did he believe that a certain toxin was not soluble in our culture media, and, as we filter off the diphtheria germs, was therefore not present in the toxin used for immunising our horses. This particular toxin we believe to be largely responsible for the post-diphtheria paralysis. We did a little work trying to confirm these results, but with no satisfactory conclusion.

"Until we have further looked into the matter we do not believe that we are warranted in making any change in our production of antitoxin. In the meantime, however, we shall be glad to have you keep us informed as to Dr. Brownlee's observations, and those of any other of your physicians bearing on this question."

The above is what the head of our Biological Board has written us, and it almost appears to us as if we had failed to make our meaning clear in respect of our opinion that the cause of the paralytic symptoms was not in any deficiency of the serum, but was due to some change in the character of the disease itself.

We should be glad if you could keep track of this matter, and in particular if you would be kind enough to make a note of the finishing number of those bulbs of serum which appear to you to be connected with any special feature in your cases, and from this we shall be able to trace the history of the serum, which may possibly give us some information on the subject.

Thanking you for your kind interest in this matter, and awaiting your comments.—We remain, Very truly yours,

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Papers on Serotherapy by members of the Belvidere Hospital Staff from the commencement of the treatment till the present day.

1. "Notes on cases of diphtheria treated with antitoxin," by E. L. Marsh, M.B. (*Glas. Med. Journ.*, March, 1895).
2. "Further notes on cases of diphtheria treated with antitoxin," by E. L. Marsh, M.B. (*Glas. Med. Journ.*, May, 1895).
3. "Diphtheria treated with antitoxin: Statistical statement of the results obtained in the City of Glasgow Fever Hospital, Belvidere," by E. L. Marsh, M.B. (*Glas. Med. Journ.*, May, 1896).
4. "Vaccinal immunity in relation to the serum treatment of small-pox, with a record of cases," by R. S. Thomson, M.B., B.Sc., and E. L. Marsh, M.B., D.P.H. (*Scot. Med. and Surg. Journ.*, August, 1897).
5. "Antistreptococcus serum: its application in the treatment of scarlatina anginosa," by Campbell S. Marshall, M.D., D.P.H. (*Glas. Hosp. Rep.*, 1899).
6. "An analytical account of fifty-seven cases of puerperal infection," by Edgar Macharg, M.D. (*Brit. Med. Journ.*, 17th February, 1900).
7. "The sero-therapeutics of plague," by John Brownlee, M.D. (*Lancet*, 17th August, 1901).
8. "On the treatment of diphtheria by the intravenous administration of antidiphtheric serum," by D. Louis Cairns, M.D. (*Lancet*, 20th December, 1902).
9. "The antitoxin treatment of diphtheria in the City of Glasgow Fever Hospital, Belvidere, during six and a half years," by John Brownlee, M.D. (*Glas. Med. Journ.*, April, 1902).
10. "Further observations on the treatment of small-pox by the serum of vaccinated heifers," by R. S. Thomson, M.D., D.Sc., and John Brownlee, M.D. (*Lancet*, 4th April, 1903).
11. "On the treatment of bubonic plague by Yersin's serum, with observations on its mode of action," by D. L. Cairns, M.D. (*Lancet*, 19th May, 1903).
12. "On the supersensitation of persons suffering from diphtheria by repeated injections of horse serum," by J. R. Currie, M.A., M.B. (*Journal of Hygiene*, 1907).
13. "Examples of the immediate and of the accelerated reactions following two injections of horse antidiphtheric serum," by J. R. Currie, M.A., M.B. (*Journal of Hygiene*, 1907).
14. "The serum disease in man after single and repeated doses," by J. R. Currie, M.A., M.B. (*Glas. Med. Journ.*, May, 1908).
15. "Abnormal reactions to horse serum in the serum treatment of cerebrospinal fever," by J. R. Currie, M.A., M.B. (*Journal of Hygiene*, 1908).